

Placental Permeability of Lead

by Stanley J. Carpenter*

The detection of lead in fetal tissues by chemical analysis has long been accepted as *prima facie* evidence for the permeability of the placenta to this nonessential trace metal. However, only a few investigations, all on lower mammalian species, have contributed any direct experimental data bearing on this physiological process. Recent radioactive tracer and radioautographic studies on rodents have shown that lead crosses the placental membranes rapidly and in significant amounts even at relatively low maternal blood levels. While it is not possible to extrapolate directly the results of these experiments to humans because of differences in placental structure and other factors, the results do serve as a warning of the possible hazard to the human embryo and fetus of even low levels of lead in the maternal system.

The transfer of lead across the human placenta and its potential threat to the conceptus have been recognized for well over a century. Abundant early evidence of this hazard came from reports that women working in lead industries commonly exhibited unusually high rates of sterility, spontaneous abortion, and stillbirths (1-3). Even before the industrial lead hazard to pregnancy was accepted and acted upon, however, lead compounds were known for their embryotoxic properties and were often used in attempts at criminal abortion (4). More reliable evidence for the permeability of the human placenta to lead began to appear in the 1930's, when chemical analytical techniques for detecting lead in blood and other tissues were developed. The early studies of Kehoe et al. (5) and of Thompsett and Anderson (6), although limited to small series and restricted ranges of gestational ages, clearly demonstrated the presence of lead in fetal tissues and left little doubt that the

human placenta was permeable to this toxic trace metal.

A more recent study by Barltrop (7) utilizing refined analytical methods, larger and better controlled series of subjects, and the technique of paired sampling of maternal blood with fetal blood and tissue has given us a much better appreciation of the extent of lead transfer to the human fetus during gestation and the distribution of lead in fetal tissues. This study, which was conducted on apparently normal humans, indicated that placental transfer of lead began as early as the 12th week of gestation and that the total lead content in fetal tissues increased throughout pregnancy. A typical adult distribution of lead was found in fetuses with highest concentrations in bone and liver but significant amounts also in the blood, placenta, brain, heart, and kidney. The total amount of lead transferred during pregnancy appeared to be relatively small, amounting to less than 300 μg , approximately the amount of lead ingested by an average adult per day. However, as pointed out by Barltrop, the location of lead within the fetus at different stages of gestation is probably of far greater importance than the total amount present at term.

*Department of Anatomy, Dartmouth Medical School, Hanover, N.H. 03755. Dr. Carpenter was a visiting scientist with the Department of Pathology, University of North Carolina, School of Medicine, Chapel Hill, N.C. 27514 during the preparation of this manuscript.

Other studies, less comprehensive than that of Barltrop, have shown that the level of lead in human umbilical cord blood, taken at delivery, ranges from 10 to 90 $\mu\text{g}/100\text{ g}$ with an average of about 13 $\mu\text{g}/100\text{ g}$ (8-11). An interesting aspect of these data was that in nearly all paired blood samples, cord blood levels were slightly lower than those of maternal blood. This observation has prompted speculation that fetal tissues might remove lead from blood more efficiently than maternal tissues (7).

In searching the literature for comparative data, one finds there have been relatively few experimental studies on the placental permeability of lead in lower mammals. Baumann (12) in 1933, was the first to demonstrate experimentally the placental transfer of lead in a mammal. She injected pregnant rats with very small doses (0.01 μg) of radioactive lead (^{212}Pb , Thorium B) and followed its distribution in the mother and fetus by whole body radio-autography. Although the methodology was primitive in comparison with that available today and the series of animals small, nevertheless, her results indicated that lead rapidly crossed the placenta (within 1 1/2 hr after injection) and localized within the fetal tissues, primarily developing bone. Other early studies in which lead was detected by chemical analysis in the fetuses and newborns of lead-treated rats (13,14) and dogs (15) confirmed the general permeability of the mammalian placenta to this element.

Further experimentation on the placental permeability of lead apparently lapsed until 1970, when McClain and Becker (16) reported briefly on the placental transport and teratogenicity of inorganic lead in rats and mice. In this study, 50 mg/kg of radioactive lead nitrate (^{210}Pb) was infused intravenously at a rate of 0.5 mg/kg-min into pregnant rats and mice during late gestation. Lead was found to cross the placenta to a limited extent during this period, homogenized fetuses containing between 0.02 and 0.30 $\mu\text{g}/\text{ml}$ 6 hr after a single administration. In 1972, the same workers (17) conducted

further experiments on rats to determine the placental permeability and teratogenicity of several organolead compounds (tetraethyllead, tetramethyllead, and trimethyllead chloride). Infusion studies with trimethyllead chloride during the late stages of gestation (day 20 of the 21-day gestation cycle) indicated that the rate of placental transfer was minimal when blood concentrations were below what they considered to be a saturation point for binding sites on maternal erythrocytes ($\sim 400\text{ }\mu\text{g}/\text{ml}$ whole blood) and was greatly increased at maternal blood concentrations above this saturation point.

The only available experimental data on the placental transfer of lead during the teratogenically critical early periods of gestation come from a recent autoradiographic study by Carpenter et al. (18). In this study pregnant golden hamsters were injected intravenously on day 7 or 8 of their 16-day gestation cycle with 20 or 50 $\mu\text{Ci}/\text{kg}$ body weight of lead ^{210}Pb nitrate (the equivalent of 2.4 and 6.1 $\mu\text{g Pb}/\text{kg}$ respectively). Autoradiographs of gestation sacs recovered as early as 15 min postinjection revealed extensive α -track labeling of the yolk sac placental membranes, the amnion, and the embryo proper. Highest levels of radioactivity in these regions occurred, however, between 1 and 4 hr postinjection. The results of this study showed that (1) during early gestation inorganic lead crosses the placental membranes rapidly and in significant amounts, even at very low maternal blood levels, and (2) that in this species the yolk sac placenta rather than the developing chorioallantoic placenta is the primary transfer site for lead. In addition, the generalized distribution of radioactivity observed in the embryos indicated that all major organ systems are exposed to lead ions during this very critical period of development.

In summing up, it is clear that while we now have a substantial body of indirect evidence for the permeability of the placenta to lead from studies on human subjects, only a few investigations, all on lower mammalian species, have contributed any basic experimental data bearing on the physiological

parameters of this process. It is not possible, of course, due to differences in placental structure and other factors, to extrapolate directly to humans placental permeability data obtained from experiments on lower mammals. Nevertheless, previous experience with many substances has shown that such data often provide a good indication of the human response. Given the difficulties and risks inherent in experimenting with toxic substances in humans, experimental animals such as the rodents and, perhaps in the future, other mammalian species phylogenetically closer to humans, will continue to be our major source of experimental data on the placental permeability and reproductive hazards of lead. In view of the increasing levels of accessible lead in our present day environment the need for more such basic research in these areas is clearly indicated. In particular, it is important that we obtain soon more information on the rate of placental transfer of lead and its relation to gestational age, maternal blood lead levels, the transfer of other cations, such as calcium and zinc, and to other physiological and environmental factors known to influence lead toxicity (19). Further research directed toward determining the actual cellular mechanisms of placental lead transfer would also be desirable. Finally, it is imperative that we learn more about the amount and distribution of lead reaching the embryo and fetus at different stages of gestation and the consequent acute and long-term pathological effects of this exposure.

REFERENCES

1. Paul, C. Étude sur l'intoxication lente par des préparations de plomb; de son influence par le produit de la conception. *Arch. Gén. Méd.* 15: 513 (1860).
2. Oliver, T. Lead poisoning and race. *Brit. Med. J.* 1: 1096 (1911).
3. Legge, T. M., and Goadby, K. W. *Lead Poisoning and Lead Absorption*. Arnold, London, 1912.
4. Taussig, F. G. *Abortion, Spontaneous and Induced*. Mosby, St. Louis, 1936.
5. Kehoe, K. A., Thammann, R., and Cholak, J. On the normal absorption and excretion of lead. IV. Lead absorption and excretion in infants and children. *J. Ind. Hyg.* 15: 301 (1933).
6. Thompson, S. L., and Anderson, A. B. The lead contents of human tissues and excreta. *Biochem. J.* 29: 1851 (1935).
7. Barltrop, D. Transfer of lead to the human fetus. In: *Mineral Metabolism in Pediatrics*. D. Barltrop and W. L. Barland, Eds. Davis, Philadelphia, 1969, pp. 135-151.
8. Horiguchi, K., Horiguchi, S., and Suekane, M. Industrial lead poisoning. I. Absorption, transportation, deposition, and excretion of lead. 6. Lead contents in organ tissues of the normal Japanese. *Osaka City Med. J.* 5: 41 (1959).
9. Scanlen, J. Umbilical cord blood lead concentrations, relationship to urban or suburban residency during gestation. *Am. J. Dis. Child.* 121: 325 (1971).
10. Harris, P. and Holley, M. R. Lead levels in cord blood. *Pediatrics* 49: 606 (1972).
11. Haas, T., et al. Die usuelle Bleibelastung bei Neugeborenen und ihren Müttern. *Zbl. Bakt. Hyg., I. Abt. Orig. B.* 155: 341 (1972).
12. Baumann, A. Zur Pharmakologie des Bleis; über die Durchlässigkeit der Placenta für Blei. *Arch. Gynäk.* 153: 584 (1933).
13. Morris, H. P., et al. The growth and reproduction of rats fed diets containing lead acetate and arsenic trioxide, and the lead and arsenic content of newborn and suckling rats. *J. Pharmacol. Exp. Therap.* 64: 420 (1938).
14. Dalldorf, G., and Williams, R. R. Impairment of reproduction in rats by ingestion of lead. *Science* 102: 668 (1945).
15. Calvery, H. O., Laug, E. P., and Morris, H. J. The chronic effects on dogs of feeding diets containing lead acetate, lead arsenate and arsenic trioxide in varying concentrations. *J. Pharmacol. Exp. Therap.* 64: 364 (1938).
16. McClain, R. M., and Becker, B. A. Placental transport and teratogenicity of lead in rats and mice. *Fed. Proc.* 29: 347 (1970).
17. McClain, R. M., and Becker, B. A. Effects of organolead compounds on rat embryonic and fetal development. *Toxicol. Appl. Pharmacol.* 21: 265 (1972).
18. Carpenter, S. J., Ferm, V. H., and Gale, T. F. Permeability of the golden hamster placenta to inorganic lead: radioautographic evidence. *Experientia* 29: 311 (1973).
19. Goyer, R. A., and Mahaffey, K. R. Susceptibility to lead toxicity. *Environ. Health Perspect.* No. 2: 73 (1972).